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# Research Progress of Piezo1, A Mechanosensitive Ion Channel Protein, in KOA

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**Abstract:** ***Knee osteoarthritis is a common orthopedic disease in the middle-aged and elderly people, with joint pain and dysfunction caused by degenerative changes of knee cartilage as the main clinical manifestations, which seriously affects the quality of life of patients. Piezo1 protein is a kind of mechanosensitive ion channel protein, whose main function is to sense and transmit mechanical signals on the cell membrane. Studies have shown that piezo1 protein mediated mechanical electrical signal transduction mechanism can induce chondrocyte apoptosis, which leads to the occurrence and development of knee osteoarthritis. This article will mainly focus on the related research of piezo1 protein in knee osteoarthritis in recent years, and provide ideas and basis for the treatment strategy research of knee osteoarthritis.***

**Keywords:** Piezo1 protein, Knee osteoarthritis, Chondrocyte apoptosis**.**

## 1. Introduction

Knee osteoarthritis (KOA), also known as knee degenerative osteoarthritis, is the most common chronic, progressive, degenerative bone and joint disease in orthopedics. It is mainly characterized by articular cartilage degeneration [1]. A large number of studies have proved that the expression of piezo1, a mechanosensitive ion channel protein, plays a key role in the apoptosis of articular chondrocytes. Piezo1 protein, as a newly discovered mechanosensitive ion channel protein, is mainly involved in the transmission of mechanical signals on the cell membrane and plays an important role in human biomechanics. Since piezo1 protein was discovered in 2010, the academic community has gradually increased and deepened its research. Piezo1 protein is stably expressed in chondrocytes that constitute articular cartilage, in addition to the respiratory system, cardiovascular system, gastrointestinal system and urinary system. After being stimulated by excessive mechanical stress, articular chondrocytes cause their own apoptosis mediated by piezo1 protein, thus promoting the occurrence and development of KOA.

## 2. Structure, Mechanism of Action and Distribution of Piezo1 Protein

In 2010, Bertrand Coste team found an ion channel protein that needs to be activated by pressure in mouse neuroblastoma cell line through experiments. According to its characteristics, it was named piezo1, meaning "pressure" [2], and together with piezo2, a highly reactive homotetrameric gene cloned from dorsal root ganglion cells, it formed the piezo ion channel protein family.

### 2.1 Piezo1 Protein Structure

Human piezo1 protein is a large transmembrane protein composed of 2521 amino acids. Its gene is located on chromosome 16, encoded by fam38a gene, and its molecular weight is about 320kda [3]. The mouse piezo1 gene is highly homologous to human. Researchers observed under high-resolution cryo electron microscopy that the three mouse piezo1 proteins were assembled in a trimeric three bladed propeller like functional structure, with a total of 114 transmembrane regions, consisting of two parts, the central pore and the peripheral paddle [4]. The carboxyl terminus of the central pore consists of about 350 amino acids, including the outer helix, the extracellular C-terminal region, the inner helix, and the intracellular C-terminal region. Piezo1 protein mechanical signal sensing is mainly closely related to the peripheral propeller blades. Each screw blade is divided into three parts, namely blade, beam and anchor rod. This special structure makes it have flexible and precise lever type mechanical functions [5-8]. When piezo1 protein channel is activated, its peripheral propeller blade performs sensitive long-distance allosteric gate control like a lever device, and makes specific responses according to different forms of mechanical stimuli [9-14].

### 2.2 Piezo1 Protein Mechanism of Action

Piezo1 protein generates an inward current when it senses mechanical stress stimulation in physiological state. When the cell membrane is depolarized, it transports cations into the cell, thus converting mechanical stress into a series of downstream cellular signals within 2ms [15]. Piezo1 protein has permeability to $Na^+$, $K^+$, $Ca^{2+}$ and $Mg^{2+}$, but its permeability to $Ca^{2+}$ is significantly higher than that of other cations [16-17], and some studies have shown that [18], piezo1 ion channel signal transduction is carried out through $Ca^{2+}$, in which $Ca^{2+}$ plays the role of the second messenger. Studies have shown that more than 25 gene mutations in piezo1 protein can be associated with some human diseases. For example, the mutant piezo1 protein allows excess calcium ions to pass through the cell membrane, resulting in the activation of downstream calcium potassium channels, and the subsequent efflux of potassium ions causes abnormal changes in intracellular osmolarity, which dehydrates red blood cells and eventually leads to hemolytic anemia [19-20].

### 2.3 Distribution of Piezo1 Protein in Human Body

Piezo1 protein is widely expressed in various organs and tissues of human body. Studies have found that [21-22], piezo1 is found in the physiological activities of brain, lung, cardiovascular system, kidney and bladder. Whasil Lee[23]

found in the experiment that piezo1 was strongly positive in chondrocytes, and the expression level was higher than that of bladder, triglyceride and skin, similar to that of lung. In the study of bone tissue cells, piezo1 protein is abundantly expressed in bone cell line mlo-y4 [24] and osteoblast cell line MC3T3-E1, and the protein molecules are distributed in granular form in the cytoplasm of MC3T3-E1 cells [25-26]. Therefore, it can be fully suspected that the expression of piezo1 ion channel is closely related to the occurrence and development of a variety of human diseases, including knee osteoarthritis.

## 3. Research Progress of Piezo1 in KOA

KOA is a degenerative disease with knee pain and dysfunction as the main manifestations under the action of a variety of factors, which can seriously even lead to paralysis, and is characterized by the progressive destruction of articular cartilage. Articular cartilage provides protection for the relative movement between bones and bears part of the mechanical load generated by body activities. Articular cartilage is mainly composed of chondrocytes and extracellular matrix, and chondrocytes are the only cell unit of articular cartilage, which maintain and shape cartilage tissue through the dynamic balance of value-added and decomposition [27]. The degeneration of knee cartilage is often due to the apoptosis of chondrocytes. Howell [28] believes that the apoptosis of articular chondrocytes plays a decisive role in the occurrence and development of knee osteoarthritis. The pH value, osmotic pressure and mechanical stress of chondrocytes in the knee joint are important factors that affect their apoptosis, among which the mechanical stress mainly including compressive stress, tensile stress, shear stress and vibration plays a crucial role in the injury mechanism of articular chondrocytes [29-30]. Studies have found that piezo1 protein is an ion channel protein involved in mechanosensation, which has the ability to sense mechanical signals and maintain the homeostasis of the cell body. After further experiments, it was found that when chondrocytes feel mechanical stimuli such as fluid shear stress, the expression of apoptosis related genes (such as B cell lymphoma/leukemia-2) will be reduced, resulting in the apoptosis of chondrocytes derived from arthritis [31-33]. Therefore, it can be considered that the apoptosis of chondrocytes caused by piezo1 protein plays an important role in the occurrence and development of human KOA.

### 3.1 Mechanism of Piezo1 Protein in Chondrocyte Apoptosis

It is known that mitochondrial dysfunction caused by excessive influx of extracellular $Ca^{2+}$ will lead to apoptosis [34]. Studies have shown that [35], after piezo1 protein is stimulated by excessive physiological load mechanical stress, $Ca^{2+}$ channels will activate and amplify $Ca^{2+}$ signals through the depolarization of chondrocytes, while piezo1 protein channels have similar functions to $Ca^{2+}$ channels, and $Ca^{2+}$ also enters the cell through piezo1 protein channels. After excessive $Ca^{2+}$ enters the cell, $Ca^{2+}$ will participate in the kinase cascade as a key messenger. Therefore, it can be seen that the $Ca^{2+}$ channel and piezo1 protein channel lead to excessive $Ca^{2+}$ influx after stress stimulation, which subsequently activates the apoptosis related kinase cascade, and finally induces chondrocyte apoptosis.

Endoplasmic reticulum stress is also an important factor in apoptosis. Caspase is a general term for a class of cysteine proteases involved in apoptosis, which can transmit apoptotic information such as abnormal mechanical stress stimuli and inflammation to the proteolytic cascade, cleave and activate other related proteases, and finally degrade intracellular targets leading to apoptosis, especially caspase-12, which is closely related to the function of endoplasmic reticulum membrane. Therefore, caspase-12 can be used as a marker of endoplasmic reticulum stress [36]. Li [37] found through experiments that under static mechanical stimulation, KOA derived chondrocytes tend to undergo late apoptosis, and the expression of piezo1 protein and caspase-12 are significantly up-regulated, and the degree of expression is positively correlated with the apoptosis rate of chondrocytes. Thus, piezo1 protein can activate apoptosis genes through caspase-12-dependent pathway and finally induce chondrocyte apoptosis.

In conclusion, piezo1 protein can be used as a promoter of chondrocyte apoptosis. After being stimulated by external overload stress, piezo1 protein channel is activated, causing a large amount of $Ca^{2+}$ influx into the cell, and then starting the apoptotic signaling cascade, causing chondrocyte mitochondrial dysfunction and endoplasmic reticulum stress, and finally leading to chondrocyte apoptosis.

### 3.2 Inhibiting Piezo1 Protein Expression to Slow Down Chondrocyte Apoptosis

It is known that after the abnormal opening of piezo1 protein channel, excessive $Ca^{2+}$ influx will lead to chondrocyte apoptosis. In order to slow down chondrocyte apoptosis, it may be an effective method to start from the direction of inhibiting piezo1 protein expression. At present, it is known that there are many methods to inhibit the overexpression of piezo1 protein.

Lawrence [38] experiment confirmed that urocortin1 can further inactivate phospholipase A2 (PLA2) by increasing the amount of cyclic adenosine monophosphate (cAMP), which can close the piezo1 protein channel in chondrocytes and protect cell apoptosis. Urocortin1 is a polypeptide composed of 40 amino acids and belongs to the corticotropin releasing factor (CRF) family. It has its presence in multiple tissue activities of the human body. For example, it can significantly inhibit the differentiation of bone marrow precursor cells into osteoclasts and reduce the expression of a variety of osteoclast markers [39]. As an important substance regulating substance metabolism and maintaining biological functions in cells, camp is the second messenger of life information transmission [40], and plays an important role in the survival of chondrocytes. PLA2 and its metabolites can regulate a variety of ion channels. In experiments, it was found that PLA2 and its metabolites in chondrocytes play a positive role in the opening of piezo1 protein channels. The experimenters combined urocortin1 with the cellular CRF-R1 receptor to increase the intracellular cAMP content, which then led to the inactivation of PLA2, and finally closed the piezo1 protein channel to protect chondrocyte apoptosis.

It has also been reported that estrogen can effectively alleviate the decrease of chondrocyte activity caused by mechanical stress stimulation [41]. G protein coupled estrogen receptor (GPER) is a kind of estrogen receptor, which has the function of specific binding to estrogen and estrogen like substances and regulating the expression of estrogen effector genes [42]. Sun [43] found that GPER can inhibit the opening of rhoa/limk/cofilin pathway and actin polymerization mediated by mechanical stress stimulation by promoting the expression of yes associated protein (Yap) and arhgap29 and the nuclear localization of Yap, and ultimately inhibit the expression of piezo1 protein. In the experiment, it was found that the number of chondrocyte apoptosis of arthritis derived cartilage in GPER group was significantly lower than that in blank group. Therefore, we can think that GPER can reduce the apoptosis of chondrocytes in koa caused by mechanical stress by inhibiting the expression of piezo1 protein.

## 4. Summary and Outlook

The pathogenesis and development mechanism of KOA is complex and diverse, and the destruction of knee joint cartilage is its main feature. As one of the most important joints in human activities, the injury caused by mechanical stress stimulation must play a decisive role. Piezo1 protein channel, a member of the mechanosensitive ion channel family, will be over opened after the knee cartilage is subjected to mechanical stimuli such as compressive stress and shear force, which will lead to a large amount of calcium ion influx, and finally make chondrocytes apoptosis. Therefore, it has great development prospects to control or even inhibit piezo1 protein channel opening as a therapeutic target to slow down the further deterioration of KOA, which is expected to provide new ideas for the basic research and clinical treatment of KOA.

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